By Dan Rubinstein
Photographs by Boaz Perlstein

A globe composed of cells coming together represents Mor Nitzan's research into reconstructing the spatial configuration of the tissue of origin out of single-cell data.
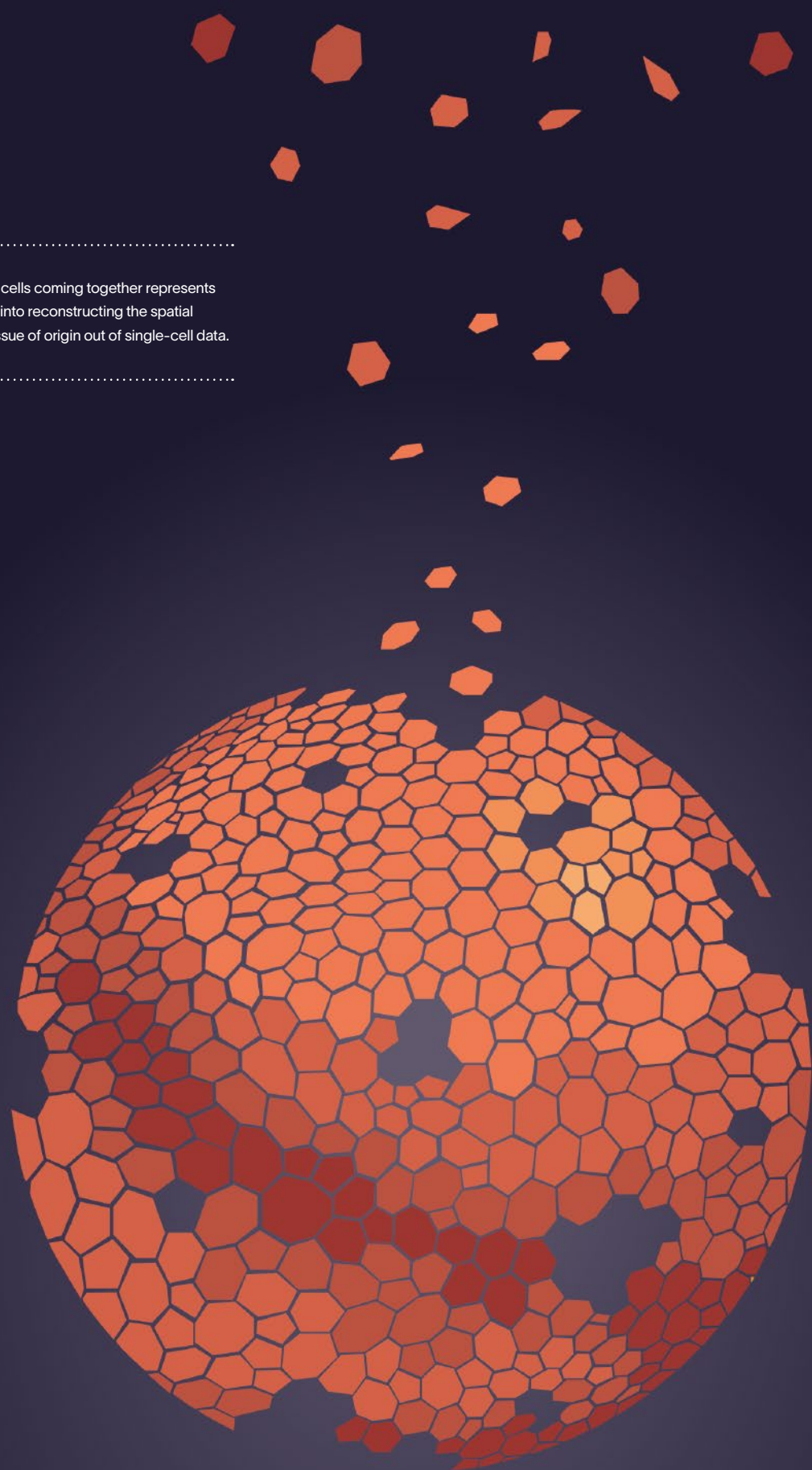
LOOKING FOR LOST

LAYERS

OF INFORMATION

Can we computationally recover spatial and temporal data about cellular behaviour to better understand complex biological systems?

Revolutionary advances in experimental biology over the past decade have given researchers the ability to take an in-depth look at individual cells. In many ways, this represents a huge scientific leap forward.

Consider the role of ribonucleic acid, or RNA, a molecule that's central to the process of converting the genetic information stored in our DNA into proteins, which are the building blocks of our cells and help carry out various functions. When a gene is active, it is transcribed into RNA; because biologists now have the ability to measure the amount and type of RNA molecules present inside a cell, they can determine which genes are active. This is giving research groups around the world access to a rapidly expanding collection of datasets through which they can study the behaviour of individual cells in diverse tissues, organisms and biological contexts, such as health and disease.

To conduct single-cell RNA-sequencing experiments, however, one must first dissociate cells from their tissues of origin. This means you can only measure cells once and can't follow their dynamics.

"You lose any spatial or temporal context you originally had," says Mor Nitzan, a researcher in the School of Computer Science and Engineering, Racah Institute of Physics and Faculty of Medicine at the Hebrew University of Jerusalem (HUJI). "You lose all of the information you could have had about how the tissue was organized, which cells were next to one another, how they communicated, even things like what the 'body plan' was for an animal in the early stages of development. spatially.
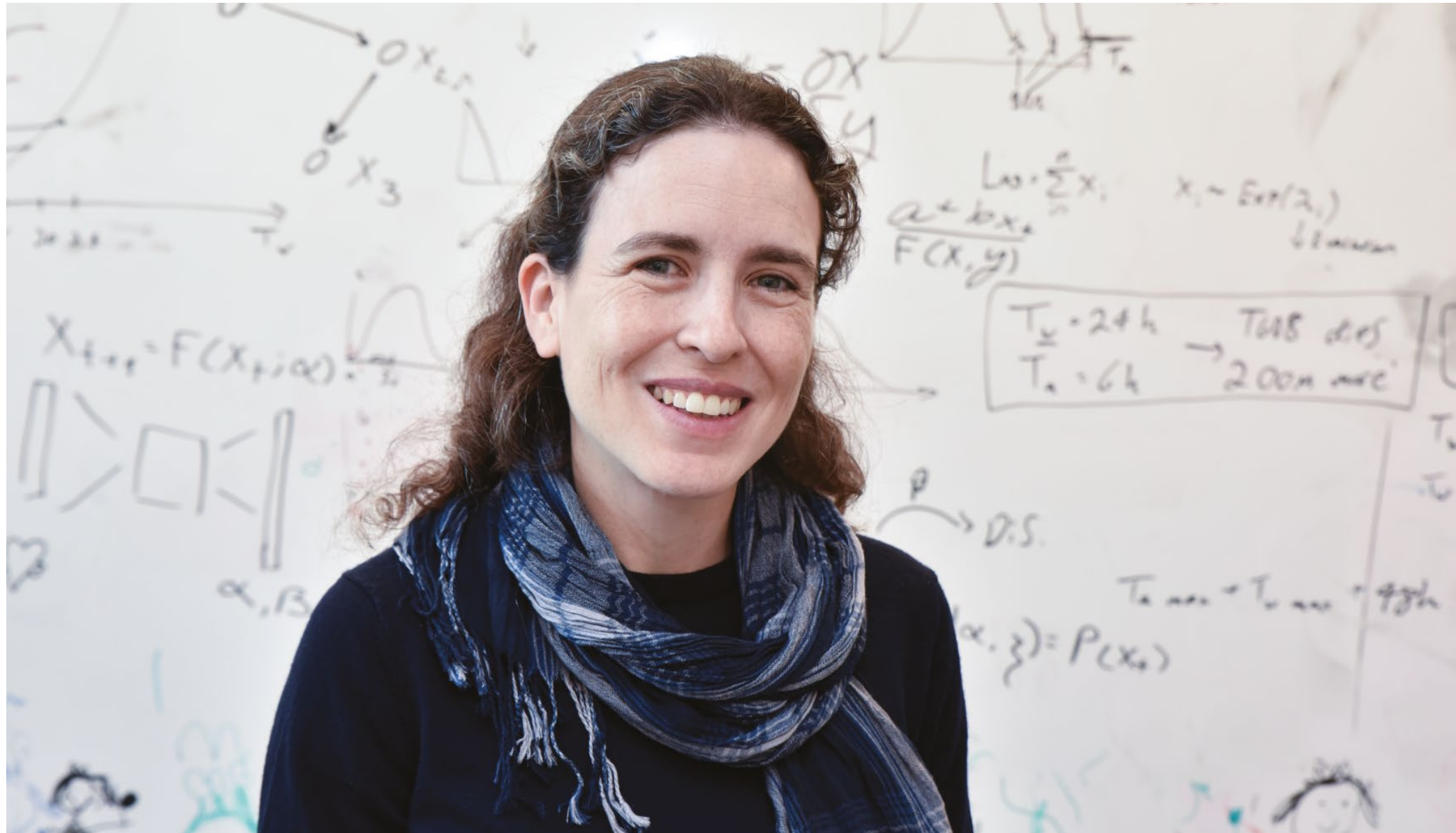
'There are a lot of very fundamental questions in biology that require access to these layers of information. In fact, many of the most interesting questions in biology and science in general have to do with spatial and temporal context.'
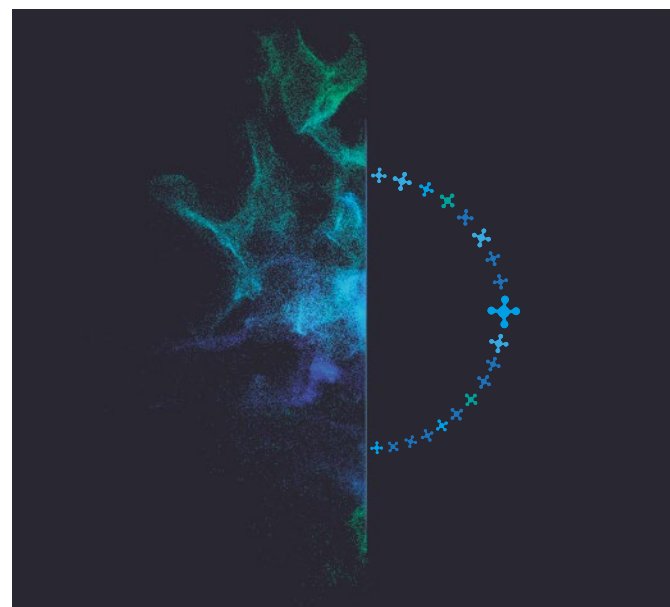
An Azrieli Early Career Faculty Fellow at the Hebrew University of Jerusalem, Nitzan (above) manipulates biological signals derived from single-cell data based on "topological priors," transforming the cloud of data on the left-hand side of this representation (left) into an easier-to-decipher configuration of cells.

DESIGNED BY PEARLCOM

"There are a lot of very fundamental questions in biology that require access to these layers of information," she continues. "In fact, many of the most interesting questions in biology and science in general have to do with spatial and temporal context."

In other words, while understanding the intimate genomic details of individual biological building blocks is a cornerstone of contemporary research, deciphering the organization and dynamics of cell *populations* could hold a key to fundamental knowledge and, ultimately, critical medical applications.

Nitzan, an Azrieli Early Career Faculty Fellow, is learning how to computationally recover the layers of data that are lost in experiments. Operating at the interface of computer science, physics and biology, with an injection of abstract mathematics, she uses computational tools, informed by dynamical systems theory and machine learning, to map the arrangement and trajectories of cells. She looks at their interaction patterns and at the division of labour within tissues, as well as the way in which cells encode information and self-organize into complex three-dimensional structures. "My group is tackling some of the core computational challenges in single-cell research," she says. "We are using this exponentially growing, complex data to ask and answer questions about the collective behaviour of biological systems."

Before beginning her undergraduate studies, Nitzan struggled to decide between pursuing physics or medicine. She chose the former — with minors in mathematics and cognitive science, at HUJI — because she was interested in basic questions about how the world works. But even though she stuck with physics, Nitzan knew she wanted to eventually use this background to address more applied questions. So she broadened her lens during her MSc and doctorate, which she completed at HUJI as well, incorporating computational biology and zeroing in on the interplay between structure and dynamics in multifaceted biological networks. That research, the latter supported by an Azrieli Graduate Studies Fellowship, was the groundwork for the work she's doing today.

"During my master's work, I started asking questions about collective phenomena," says Nitzan, "about how many small, dynamic systems come together and interact with each other, in a networked way, and display complex behaviours that aren't possible for individual systems." She realized, after moving on to her PhD with professors Hanah Margalit and Ofer Biham, that it would be powerful to not only model and test these questions in a "bottom-up, physics-based" way, but also to apply computer science techniques and use available data to inform her models — to combine methodologies and start looking at the bigger picture. Nitzan further developed this amalgamated approach during a postdoctoral fellowship at HUJI and the Broad Institute of MIT and Harvard in 2017 with professors Nir Friedman and Aviv Regev, and a year later as a John Harvard Distinguished Science Fellow and James S. McDonnell Fellow at Harvard. When she returned to HUJI in 2020 as a faculty member, it formed the backbone of her research.

Today, leading a group of about 10 researchers, from undergraduates to postdocs, and equipped with a European Research Council grant worth nearly 1.5 million Euros, Nitzan remains focused on developing computational methods to infer the underlying structure and function of biological systems and formulate mathematical models drawn out from countless biological details. Although they are abstract representations of physiological systems, these models aim to simplify and help researchers make sense of elaborate phenomena. For instance, how do cells discriminate between different environments and prepare for future challenges they may face? How do they process complex information? And how do cells divide labour to perform collective tasks?

"They're not individual units," says Nitzan. "They have to work together, transfer information and self-organize into multicellular 3D structures with different functions. We want to find out how cells make these processes robust and efficient."

Nitzan and her students are working on a spectrum of projects, ranging from theoretical research to collaborations with experimental biologists. But most of their work falls

somewhere in the middle and starts with a sprawling array of data. And computationally recovering the spatial configuration of cells within their tissue of origin is only step one.

The greater task, Nitzan explains, is disentangling layers of spatial and temporal information from each other, *manipulating* layers (enhancing one, filtering out another) and virtually shifting cell states across space and time. This method — in effect, conducting virtual experiments, using mathematical models — allows her, for example, to predict cellular response to the perturbations of drugs. Moreover, even if a cell has only been exposed to one drug, the same approach can be used to infer how that cell will respond to a different drug, or the same drug administered at a different time of day.

"We can computationally or virtually shift cells across time, across space, across perturbations, to get predictions on how they'd behave and what the response would be," she says. "And we can do so in a much more scalable way than what would be possible in biological experiments, which have a lot more limitations in terms of time and budget, beyond the fact that some experiments are simply not feasible."

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One of the holy grails of this type of research involves cellular populations that are not healthy, as is the case with cancer. Pharmaceutical researchers want to discover which drugs to introduce to make these cells or tissues healthy. A better understanding of the common cellular mechanisms that drive the progression of cancer and other diseases, and the ability to accurately predict which mechanisms might be more vulnerable to interventions, says Nitzan, "will allow you to design effective treatments for different types of diseases and even to tailor them to individuals, thinking about this ambitiously, for particular conditions.

"I'm very excited about the ability to do something that I can connect back to the real world. I love the abstract, mathematical aspects of the research, but it is also very important for me to think and contribute to an understanding of natural systems, specifically in a biological or medical context."

Nitzan thinks "deeply and carefully about the questions before her and always manages to put her finger on the crux of the problem," says collaborator Klaas Mulder, a researcher at Radboud University

in the Netherlands whose lab investigates the mechanisms underlying human epidermal stem cell renewal. "The work she and her co-workers are doing can certainly have an impact on health applications and interventions. Yet I think what will actually make a difference for the future is the fact that the approaches her lab develops empower other researchers to address their challenges in new and unexpected ways. That, I believe, is the real influence Mor has, not only on the single-cell genomics field, but far beyond that through the uptake of single-cell approaches and the computational tools by much wider scientific communities."

The abundance of single-cell data that Nitzan has at her disposal represents both an opportunity and a challenge. It keeps flowing from research projects around the world, and much of it can be downloaded with the push of a button. But it's "noisy" and confusing, she says, and it can be challenging to transform it or use it to answer the questions she's really interested in.

This is by no means a problem that's unique to her field. Human beings have to constantly disentangle layers of information to make decisions, and we are increasingly tapping into modelling and machine learning to push through that data bottleneck. "The questions I'm asking are basic, and there are interesting analogies to how our minds work and how we can process huge amounts of information," says Nitzan. "It's the same for biological data and what's meaningful to know about cellular populations. It's fine that you can measure the expression of every gene in a cell for hundreds of thousands of cells experiencing hundreds of different conditions, but to answer fundamental questions and make predictions that are relevant for medical applications, you don't need all these individual bits of information — you need to be able to *integrate* all that complex information into meaningful nuggets."

Thinking about this puzzle and trying to come up with the right mathematical language to describe and simplify complex systems is the most engaging aspect of this work for Nitzan. She loves the creativity. ("Although most of the technicalities of the math involved go beyond my level of comprehension," says Mulder, "Mor always ensures that we understand what we need to be able to assess the results.") But now that she's a principal investigator, Nitzan has another dynamic system to navigate — the community of students and postdocs in her lab. She is busy providing mentorship and guidance, not to mention teaching, writing papers and grant proposals, and trying to maintain some work-life balance.

"I'm never up to speed with everything I want to do," she says. "It's always overflowing. But I'm dedicated not only to the research itself, but also to steering the group toward creative, effective and successful directions and making sure that everybody is supported in a way that's tailored toward helping them find and pursue their scientific passion."

In her lab and in her research, Nitzan pays attention to individual people and individual cells, but she knows the real breakthroughs will come from the community as a whole. ▲●■
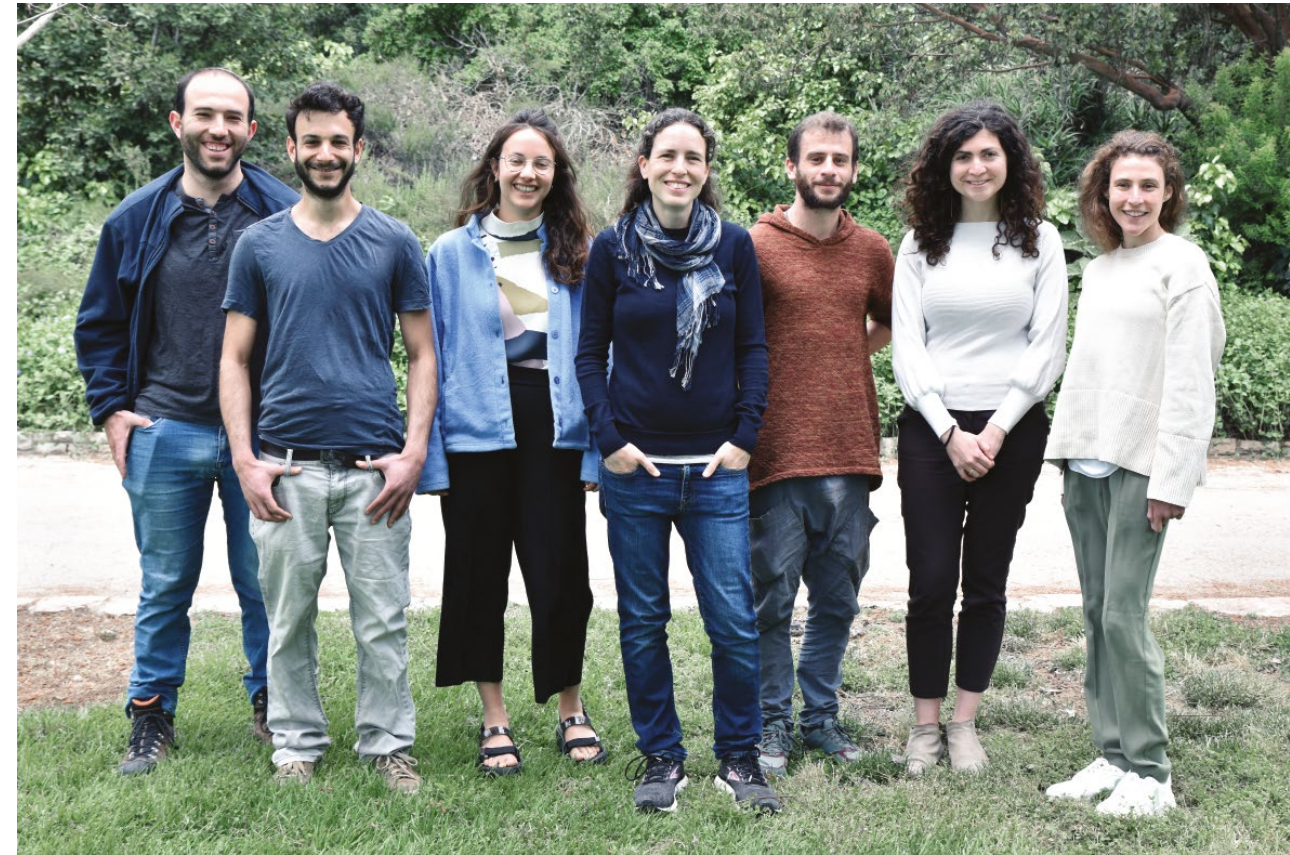
Members of Nitzan's research group include (left to right) undergraduate researcher Yehuda Mescheloff, MSc student Rotem Tal, MSc student Michal Erez, Nitzan, and PhD students Hagai Rappeport, Sima Dubnov and Zoe Piran.

IGNITING THE VOLUNTEERISM GENE

When Mor Nitzan was a PhD student in physics and computational biology at the Hebrew University of Jerusalem (HUJI), she was an Azrieli Graduate Studies Fellow. The fellowship opened several different doors for her. Beyond the generous funding, it provided a community of support. It gave her a group of young academics to talk to and bounce ideas off, conversations that helped shape the direction of Nitzan's research journey. The fellowship also had a volunteer component, which prompted her to co-start a program, A Taste of Science, that introduces high school students in Israel to role models in different fields and encourages them to consider university studies and careers in science.

Nitzan handed that program over to HUJI when she left for a postdoc in the United States, but it has remained active over the past half-dozen years, showing thousands of high school students the opportunities they might have. And despite her own demanding career, Nitzan hasn't lost her zeal for educational outreach and volunteer work that the Azrieli Fellows Program awoke. She organizes and is involved with a range of activities focused on women in science, including events designed to prepare female PhDs for postdoctoral positions, and serves as the gender equity coordinator in HUJI's School of Computer Science and Engineering as well as a member of the university's overarching gender equity committee.

"There's an underrepresentation of women in science, which is especially apparent in fields such as physics and computer science," says Nitzan. "One of the most problematic aspects of this is that the percentage of women decreases as you get to advanced stages of an academic career, to PhDs and postdocs and faculty positions."

Increasing the diversity of role models is one way to help close this gap. Making women and other underrepresented groups aware of their opportunities — and providing or pointing the way to specific supports — is another. So is changing the system itself, to level the playing field. And it's not just about equity for the sake of equity. Diversity in science is important because successful research needs access to the vast array of brain power out there in the world.

"Any improvement makes the university better and the research community stronger," says Nitzan. "It's true for my scientific community and the scientific community at large. And it's not just about women — it's a general statement about diversity and the ability to draw from the entire population and not only subsets of it." ▲●■